

Review

NMDA receptors as targets for drug action in neuropathic pain

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Abstract

Hyperalgesia and allodynia following peripheral tissue or nerve injury are not only due to an increase in the sensitivity of primary afferent nociceptors at the site of injury but also depend on NMDA receptor-mediated central changes in synaptic excitability. Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site (competitive), strychnine-insensitive glycine site (glycine_B), polyamine site (NR2B selective) and phencyclidine site located inside the cationic channel. Unfortunately, most agents which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and motor incoordination. There is now, however, considerable evidence that moderate affinity channel blockers, glycine_B and NR2B selective antagonists show a much better profile in animal models than high affinity channel blockers and competitive NMDA receptor antagonists. These “therapeutically” safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the utility of their combination with opioids in the treatment of chronic pain. The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine. Peripheral NMDA receptors offer a very attractive target for NMDA receptor antagonists that do not cross the blood brain barrier in inflammatory and visceral pain. Such agents might be predicted to be devoid of CNS side effects at doses producing powerful antinociception at peripheral NMDA receptors. © 2001 Elsevier Science B.V. All rights reserved.

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1. Glutamate in chronic pain

Despite intensive research on the neurobiological mechanisms of chronic pain, this therapeutic area remains one of the least satisfactorily covered by current drugs. Mal-functioning of glutamatergic neurotransmission has been implicated in a wide variety of neurological diseases such as acute stroke and trauma, chronic neurodegenerative diseases, epilepsy, schizophrenia and depression (see Parsons et al., 1998). Of particular relevance for this review is the involvement of glutamate in diseases reflecting long-term plastic changes in the central nervous system (CNS) such as chronic pain, opioid tolerance, dependence and addiction (Bennett, 2000).

Glutamate activates two major classes of receptors: ionotropic and metabotropic. Ionotropic receptors are classified into three major subclasses: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA). There is considerable pre-

clinical evidence that hyperalgesia and allodynia following peripheral tissue or nerve injury is not only due to an increase in the sensitivity of primary afferent nociceptors at the site of injury but also depends on NMDA receptor-mediated central changes in synaptic excitability (Dickenson, 1990; Dickenson et al., 1997; Ren, 1994; Sandkuhler and Liu, 1998).

2. NMDA receptor antagonists

Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site (competitive), strychnine-insensitive glycine site (glycine_B), polyamine site (NR2B selective) and phencyclidine site located inside the cationic channel (see Parsons et al., 1998). NMDA channel blockers act in an uncompetitive “use-dependent” manner, meaning that they only block the channel in the open state.

Unfortunately, antagonists which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and

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motor incoordination, as they also impair normal synaptic transmission—a two-edged sword. The challenge has therefore been to develop NMDA receptor antagonists that prevent the *pathological* activation of NMDA receptors but allow their *physiological* activation.

2.1. Uncompetitive antagonists

It has been suggested that uncompetitive NMDA receptor antagonists with rapid unblocking kinetics but somewhat less pronounced voltage-dependency than Mg^{2+} should be able to antagonise the pathological effects of the sustained, but relatively small increases in extracellular glutamate concentration, but, like Mg^{2+} , leave the channel as a result of strong depolarisation following physiological activation (e.g. Parsons et al., 1999). Thus, uncompetitive NMDA receptor antagonists with moderate, rather than high affinity may be desirable. Memantine, amantadine, ketamine and dextromethorphan are clinically used agents which belong to this category (Hewitt, 2000; Schmid et al., 1999; Gordon et al., 1999). Others such as remacemide, (*S*)- α -phenyl-2-pyridineethanamine dihydrochloride (ARL 15896AR), bis-3-fluor-phenyl-propanamine (NPS-1506) and possibly the cannabinoid Dexamibinol (HU-211) are at different stages of clinical development (see Fig. 1 and Parsons et al., 1998).

Although the hypothesis underlying the ability of low affinity open channel blockers to differentiate between phasic physiological and tonic pathological activation of NMDA receptors during ischaemia has gained relatively wide acceptance (Chen et al., 1992; Rogawski, 1993; Kornhuber and Weller, 1997; Mealing et al., 1997; Parsons

et al., 1999), it is still unclear how such compounds could differentiate between normal and abnormal synaptic activation of NMDA receptors. One possible explanation is that the forms of synaptic activity in the two states are different. Long-term potentiation is a biophysical model for the patterns of NMDA receptor-dependent synaptic activity underlying memory formation (Collingridge and Bliss, 1995; Herron et al., 1986) and is normally induced by delivering a high frequency tetanic stimulus (typically 100 Hz for 1 s). Under such conditions, drugs such as memantine can leave the open NMDA receptor channel during the stimulus burst. Indeed very high concentrations of memantine are required to block the induction of long-term potentiation both in vivo and in vitro (Barnes et al., 1996; Frankiewicz et al., 1996). Wind-up is a biophysical model for the patterns of synaptic activity underlying the induction of chronic pain states (Dickenson, 1990; Dickenson et al., 1997; Ren, 1994) and is normally induced by repetitive stimulation at much lower frequencies but for longer periods (typically 0.5 Hz for 5–10 s). Most NMDA receptor antagonists block this form of synaptic activity, including therapeutically relevant doses of moderate affinity uncompetitive antagonists. It should be noted, however, that the relevance of wind-up for the induction of chronic pain states has recently been questioned because wind-up, central sensitisation and hyperalgesia are not the same phenomena, even though they share some common properties (Herrero et al., 2000). Long-term depression is also an NMDA receptor-dependent biophysical model of synaptic plasticity that is induced by lower frequency stimulation over longer periods of time (Bear and Malenka, 1994; Malenka, 1994; Baudry, 1996) and requires less pro-

Uncompetitive Antagonists

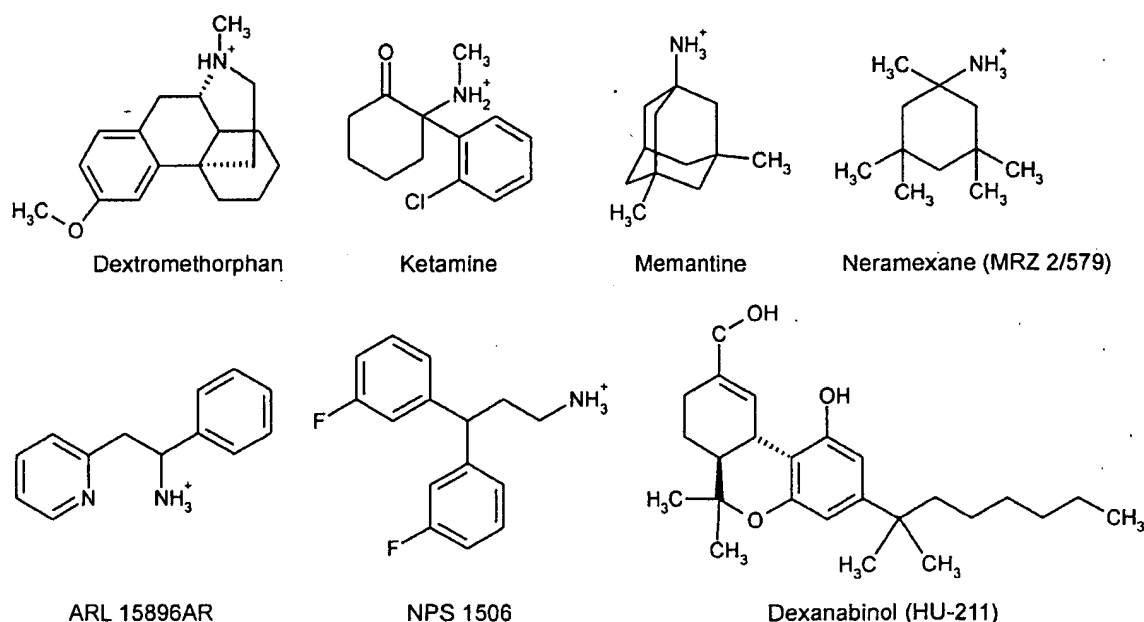


Fig. 1. Uncompetitive antagonists.

nounced increases in intracellular Ca^{2+} than long-term potentiation (Artola and Singer, 1993; Hansel et al., 1996). It seems likely that during the induction of wind-up or long-term depression for each successive NMDA-receptor mediated EPSP, the duration is too short and the degree of depolarisation too low to allow sufficient relief of blockade by low affinity open channel blockers. In other words, such compounds can block moderate NMDA receptor activation underlying, e.g. chronic pain states (modelled by wind-up) or the development of drug tolerance (possibly modelled by long-term depression) but do not block stronger NMDA receptor activation underlying memory formation (modelled by long-term potentiation).

Whatever the biophysical mechanism underlying this difference, therapeutically relevant doses of memantine selectively block formalin-induced tonic nociceptive responses in rats (Eisenberg et al., 1993) and produce a prophylactic antinociceptive effect against carrageenan-induced hyperalgesia (Neugebauer et al., 1993; Eisenberg et al., 1994) at doses devoid of side effects. Memantine also blocks and reverses thermal hyperalgesia and mechanical allodynia in rat models of painful mononeuropathy without obvious effects on motor reflexes following systemic (Carlton and Hargrett, 1995; Eisenberg et al., 1995) and local spinal administration (Chaplan et al., 1997). Interestingly, in a recent study, memantine produced powerful inhibition of wind-up after selective ligation of the L5/L6 spinal nerves with little effect in sham controls in contrast to dizocilpine ((+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten 5,10 imine, (+)MK 801), which non-selectively blocked responses (Suzuki et al., 2001). Clinical trials with memantine in post herpetic neuralgia and diabetic neuropathic pain syndrome are presently underway. Ketamine is also effective in various animal models of hyperalgesia and allodynia and, like memantine, has been reported to have antinociceptive effects in some of these models at doses devoid of obvious side effects (Mao et al., 1993; Qian et al., 1996; Ren et al., 1992). Others,

however, have reported that the effects of ketamine are only seen at doses producing ataxia (Chaplan et al., 1997; Laird et al., 1995; Yaksh, 1989). This may be related to its somewhat higher potency and associated slower unblocking kinetics.

2.2. Glycine site antagonists

Another promising target for NMDA receptor antagonism is the glycine_B modulatory site (for review see Danysz and Parsons, 1998). Full antagonists of this site may offer a promising therapeutic profile due to their ability to increase NMDA receptor glycine-dependent desensitization. Prolonged repetitive activation of NMDA receptors would be effectively reduced at concentrations having little effect on more transient activation as the time course for full desensitization is quite long (tau several hundred milliseconds). This property may also allow such compounds to differentiate between various forms of NMDA receptor-mediated synaptic plasticity, e.g. block long-term depression and wind-up at concentrations having less effect on long-term potentiation. This idea is supported by recent data indicating that systemically active glycine_B antagonists have good therapeutic indices following systemic administration in models of hyperalgesia (Vaccarino et al., 1993; Millan and Seguin, 1994; Laird et al., 1996; Quartaroli et al., 1999) as anxiolytics, possible anti-psychotomimetics, neuroprotective agents in models of focal ischaemia and trauma, and anti-epileptics (see Danysz and Parsons, 1998). In contrast to high affinity uncompetitive antagonists, glycine_B antagonists do not have psychotomimetic effects (Löscher et al., 1994; Karcz-Kubicha et al., 1999) and have even been reported to possess antipsychotic activity (Bristow et al., 1995, 1996). They have no negative effects on learning at doses effectively blocking NMDA receptor *in vivo* (see Danysz and Parsons, 1998). Finally, unlike high affinity uncompetitive antagonists such as (+)-MK-801 and phencyclidine

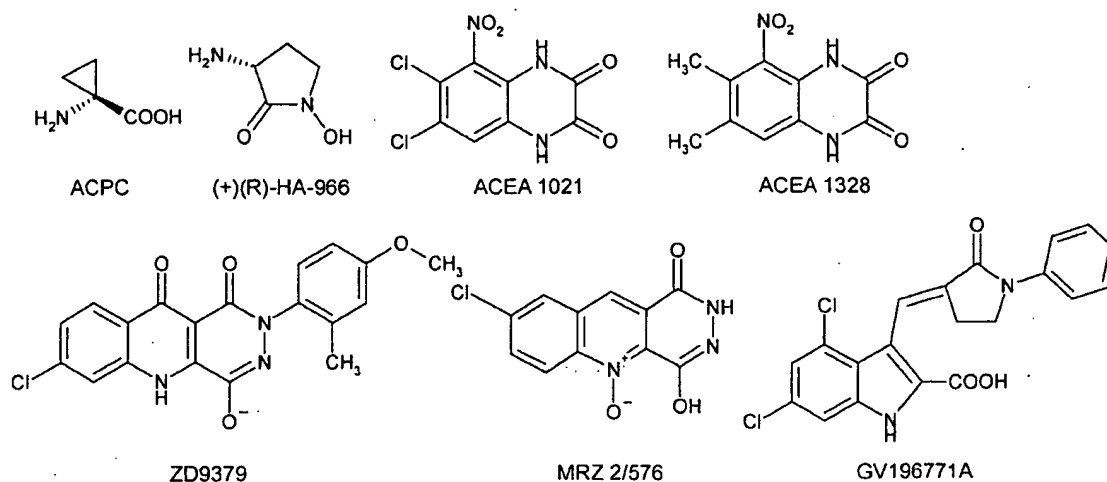


Fig. 2. Glycine site antagonists.

(PCP), even very high doses do not cause any neurodegenerative changes in the cingulate/retrosplenial cortex of rats (Chen et al., 1993; Hargreaves et al., 1993; Berger et al., 1994).

The glaxo compound GV 196771A is presently in phase I clinical trials for pain (see Fig. 2). This glycine_B antagonists was effective in blocking the development of hyperalgesia following chronic sciatic nerve ligation in rats when given orally at 3 mg/kg twice daily for 10 days. GV 196771A also dose-dependently reversed established hyperalgesia for up to 8 h. The therapeutic profile was promising in as much as the second phase of formalin-induced hyperalgesia was antagonized with an ID₅₀ of 0.6 mg/kg p.o. whereas 10 mg/kg had no effect on the first phase (Quartaroli et al., 1999). Other systemically active glycine_B antagonists presently under development and with therapeutic potential in the treatment of pain include 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021, Licostinel, Lutfy et al., 1995, 1996), 7-Chloro-4-hydroxy-2-(4'-methoxyphenyl)-6'-methyl-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (ZD9379, Tatlisumak et al., 1998) and 8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridazinol[4,5-]quinoline-5-oxide choline (MRZ 2/576, Parsons et al., 1997).

2.3. NR2B selective antagonists

Subtype selective agents may also offer a promising approach to minimize side effects as agents would not produce maximal inhibition of responses of neurones expressing heterogeneous receptors. Thus, cortical and hippocampal neurones express both NR2A and NR2B receptors in approximately similar proportions, but very little NR2C or NR2D. NR2B selective agents therefore block NMDA receptor mediated responses of such neurones to a maximal level of around 30–50% of control. The NR2B selective agent (1*S*,2*S*)-1-(4-hydroxy-phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol (CP-101,606, see Fig. 3) has indeed been reported to be effective in suppressing hyperalgesia in animal models of chronic pain (carrageenan, 4-Phorbol-12-myristate-13-acetate (PMA), capsaicin and allodynia in neuropathic rats) at doses devoid of negative side effects in motor co-ordination or behaviour (Taniguchi et al., 1997; Boyce et al., 1999). A good separation was also reported for (*R*-(*R*^{*},*S*^{*})-(4-hy-

droxyphenyl)-methyl-4-(phenylmethyl)-1-piperidinepropanol ((±)-Ro 25-6981, Boyce et al., 1999) indicating that NR2B selective antagonists may also have clinical utility for the treatment of neuropathic and other pain conditions in man with a reduced side-effect profile. Unfortunately, several NR2B selective agents seem to block human ether-a-go-go-related gene (HERG)-mediated K(+) currents and may thereby produce severe side effects by increasing the cardiac Q/T interval.

3. Wind-up

More recent studies have addressed the issue whether it is possible to reproduce clinically the well characterized inhibition of wind-up seen with NMDA receptor antagonists in animal models. Dextromethorphan and ketamine, but not morphine significantly reduced both the area of secondary hyperalgesia and temporally summated 'wind-up-like pain' to repeated von Frey filament stimulation in healthy human volunteers with experimental first degree burn injury (Ilkjaer et al., 1997; Mikkelsen et al., 1999). Ketamine was also effective in reducing secondary hyperalgesia and allodynia induced by capsaicin in a double-blind, placebo-controlled, human experimental study (Andersen et al., 1996). Similar effects on "wind-up-like" pain were previously reported with i.v. ketamine and oral dextromethorphan in healthy volunteers, rating the intensity of summated second pain in response to repeated painful electric shocks and heat pulses (Price et al., 1994; Arendt Nielsen et al., 1995).

4. Opioid tolerance

It is believed that phenomena such as sensitisation, tolerance and drug-dependence might also involve synaptic plasticity. In fact, numerous studies indicate that NMDA receptor antagonists block sensitisation to amphetamine and cocaine as well as tolerance and dependence to ethanol and opioids in animal models (Trujillo, 2000; Trujillo and Akil, 1991, 1995; Pasternak and Inturrisi, 1995; Mao, 1999). Recent studies indicate that the uncompetitive NMDA receptor antagonists dextromethorphan, memantine and MRZ 2/579 (1,3,3,5,5-pentamethylcyclohexylamine, neramexane) are not only able to prevent the development

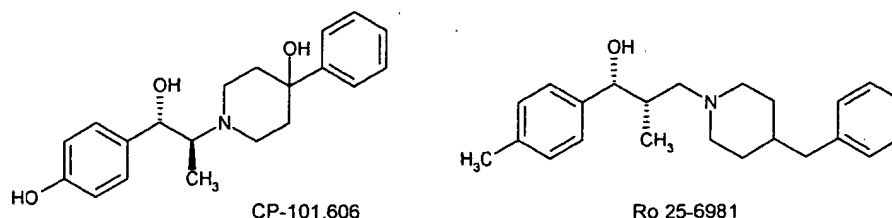


Fig. 3. NR2B selective antagonists.

of morphine tolerance, but also reverse established tolerance even in the continuing presence of this opioid and prevent the expression of withdrawal symptoms in rats (Popik and Skolnick, 1996; Popik and Danysz, 1997; Popik and Kozela, 1999; Houghton et al., 2001). Moreover, acquisition of i.v. morphine self-administration in drug- and experimentally naive mice was inhibited by pretreatment with MRZ 2/579 (Semenova et al., 1999). Likewise, systemically active glycine_B antagonists attenuate both physical dependence to morphine and the development of tolerance to the antinociceptive effects of opioids following repeated administration. Thus, 5-nitro-6,7-dimethyl-1,4-dihydro-2,3-quinoxalinedione (ACEA-1328) and ACEA-1021 completely blocked tolerance to morphine-induced antinociception in the tail flick test in mice, without affecting the basal nociceptive response or potentiating morphine-induced antinociceptive effects (Lutfy et al., 1995, 1996; Pasternak and Inturrisi, 1995). In contrast, the ability of MRZ 2/576 to attenuate morphine tolerance was associated with an increased morphine peak analgesia and duration in the tail-flick test (Popik et al., 1998; Belozertseva et al., 2000a,b). Administration of either (+)-(3*R*)-3-Amino-1-hydroxypyrrolidin-2-one ((+)-HA-966) or morphine alone was devoid of effects on the mechanical hyper responsiveness to von Frey hair stimulation in a model of chronic constriction injury whereas combined administration of (+)-HA-966 (2.5 mg/kg s.c.) and morphine (0.25, 0.5 and 1 mg/kg i.v.) dose-dependently increased the mechanical response thresholds (Christensen, 1999). This effect was naloxone-sensitive and was not accompanied by motor deficits (*ibid.*). When given alone 1-aminocyclopropane-carboxylic acid (ACPC, 50 and 150 mg/kg) had no analgesic actions in the tailflick assay and did not change morphine's potency in naive mice (Kolesnikov et al., 1994). However, chronic administration of this "functional" NMDA receptor antagonist both prevented and reversed morphine tolerance (*ibid.*). Also supportive for the role of NMDA receptors in opioid dependence is the finding that the opioid methadone (used in the therapy of addiction) also blocks NMDA receptors (Ebert et al., 1995) and that both the D- and L-isomer inhibit [³H](+)-MK-801 binding to spinal cord membranes at therapeutically relevant concentrations: *K_d*s of 2.6 and 2.8 μ M (Gorman et al., 1997). However, a recent paper concluded that NMDA antagonism does not contribute to the mechanism of D-methadone antinociception in vivo as both the antinociceptive and antagonism of responses to micro-iontophoretic NMDA were reversed by the opioid receptor antagonist naloxone (Chizh et al., 2000).

On a similar line, there are some indications that NMDA receptor activation may have a critical role in the mechanisms underlying the reduced effectiveness of opioids in chronic neuropathic pain states. For example, the antinociceptive effects of morphine are reduced in nerve-injured rats in the absence of daily exposure to morphine and this

effect can be prevented by treatment with (+)-MK-801 (Mao et al., 1995). This may be due to the fact that NMDA receptor activation attenuates opioid receptor G protein coupling via activation of protein kinase C (Cai et al., 1997; Fan et al., 1998) and that opioid receptor activation increases NMDA receptor function via phosphorylation (Swope et al., 1999).

Taken together with the above mentioned effects of some NMDA receptor antagonists in models of chronic pain, these data indicate the utility of the combined use of therapeutically safe NMDA receptor antagonists with opioids in the treatment of chronic pain (Eide et al., 1995; Elliott et al., 1995; Bennett, 2000). The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine. Indeed, this approach has recently been pursued by Algos with morphidex (a combination of morphine and dextromethorphan), which is in phase III clinical trials for the treatment of chronic pain (see Parsons et al., 1998).

5. Peripheral NMDA receptors

Recent data indicate that peripheral NMDA receptors are also involved in inflammatory somatic and visceral pain. Peripheral glutamate receptors are associated with unmyelinated axons (Carlton et al., 1995) and the number of somatic sensory axons containing ionotropic glutamate receptors increases during peripheral sensitization due to inflammation (Carlton and Coggeshall, 1999; Coggeshall and Carlton, 1999). Subcutaneous administration of formalin into the plantar surface of rat hindpaws causes an increase in glutamate and aspartate concentrations in this tissue (Omote et al., 1998). Local injection of glutamatergic agonists to glabrous skin evokes pain-related behaviours in rats (Carlton et al., 1995; Jackson et al., 1995; Zhou et al., 1996) and peripherally administered glutamate receptor antagonists can prevent this effect as well as formalin or inflammation-induced hyperalgesia (Jackson et al., 1995; Davidson et al., 1997; Carlton et al., 1998; Davidson and Carlton, 1998). Similar effects have also been seen in experiments using local administration to the knee joint cavity in rats (Lawand et al., 1997). Local injection of ketamine into the skin on one calf of 10 healthy volunteers reduced primary and secondary hyperalgesia following a local experimental first degree burn injury, supporting the role of peripheral NMDA receptors in mediating secondary hyperalgesia in humans (Warneke et al., 1997).

Immunohistochemical studies indicate that NR1 subunits are expressed on the cell bodies and peripheral terminals of primary afferent nerves innervating the colon. Moreover, colorectal distension activation of single afferents in decentralised pelvic nerves was inhibited by me-

mantine, indicating that peripheral NMDA receptors are important in normal visceral pain transmission, and may provide a novel mechanism for development of peripheral sensitization and visceral hyperalgesia (McRoberts et al., 2001). Increases in blood pressure evoked by graded distension of the normal ureter was potentially blocked by the glycine_B antagonist MRZ 2/576, suggesting that NMDA receptors are involved in the processing of acute nociceptive inputs from viscera (Olivar and Laird, 1999). Moreover, the effective dose (ID₅₀ = 0.2 mg/kg) was at least 10-fold lower than that known to antagonize NMDA receptors in the CNS (Parsons et al., 1997), indicating that peripheral NMDA receptors may also be involved in this effect.

6. Conclusions

(1) NMDA receptor antagonists which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and motor incoordination, and they also impair normal synaptic transmission—a two-edged sword.

(2) The challenge has therefore been to develop NMDA receptor antagonists that prevent the pathological activation of NMDA receptors but allow their physiological activation.

(3) There is now considerable evidence that moderate affinity channel blockers, glycine_B and NR2B selective antagonists show a much better profile in animal models of chronic pain than high affinity channel blockers and competitive NMDA receptor antagonists.

(4) These therapeutically safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the utility of their combination with opioids in the treatment of chronic pain. The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine.

(5) The involvement of peripheral NMDA receptors in inflammatory and visceral nociception offers a very attractive target for NMDA receptor antagonists that do not cross the blood brain barrier. Such agents might be predicted to be devoid of CNS side effects at doses producing powerful antinociception at peripheral NMDA receptors.

References

- Andersen, O.K., Felsby, S., Nicolaisen, L., Bjerring, P., Jensen, T.S., Arendt Nielsen, L., 1996. The effect of ketamine on stimulation of primary and secondary hyperalgesic areas induced by capsaicin—a double-blind, placebo-controlled, human experimental study. *Pain* 66, 51–62.
- Arendt Nielsen, L., Petersenfelix, S., Fischer, M., Bak, P., Bjerring, P., Zbinden, A.M., 1995. The effect of *N*-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth. Analg.* 81, 63–68.
- Artola, A., Singer, W., 1993. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. *Trends Neurosci.* 16, 480–487.
- Barnes, C.A., Danysz, W., Parsons, C.G., 1996. Effects of the uncompetitive NMDA receptor antagonist memantine on hippocampal long-term potentiation, short-term exploratory modulation and spatial memory in awake, freely moving rats. *Eur. J. Neurosci.* 8, 565–571.
- Baudry, M., 1996. Similarities and contrasts between cerebellar LTD and hippocampal LTP. *Behav. Brain Sci.* 19, 435.
- Bear, M.F., Malenka, R.C., 1994. Synaptic plasticity: LTP and LTD. *Curr. Opin. Neurobiol.* 4, 389–399.
- Belozertseva, I.V., Danysz, W., Bessalov, A.Y., 2000a. Effects of short-acting NMDA receptor antagonist MRZ 2/576 on morphine tolerance development in mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 361, 573–577.
- Belozertseva, I.V., Danysz, W., Bessalov, A.Y., 2000b. Short-acting NMDA receptor antagonist MRZ 2/576 produces prolonged suppression of morphine withdrawal in mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 361, 279–282.
- Bennett, G.J., 2000. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. *J. Pain Symptom Manage.* 19, 2–6.
- Berger, P., Farrel, D., Sharp, F., Skolnick, P., 1994. Drugs acting at the strychnine-insensitive glycine receptor do not induce HSP-70 protein in the cingulate cortex. *Neurosci. Lett.* 168, 147–150.
- Boyce, S., Wyatt, A., Webb, J.K., O'Donnell, R., Mason, G., Rigby, M., Sirinathsinghji, D., Hill, R.G., Rupniak, N.M.J., 1999. Selective NMDA NR2B antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunit in dorsal horn. *Neuropharmacology* 38, 611–623.
- Bristow, L.J., Landon, L., Saywell, K.L., Tricklebank, M.D., 1995. The glycine/NMDA receptor antagonist, L-701,324 reverses isolation-induced deficits in prepulse inhibition in the rat. *Psychopharmacology* 118, 230–232.
- Bristow, L.J., Flatman, K.L., Hutson, P.H., Kulagowski, J.J., Leeson, P.D., Young, L., Tricklebank, M.D., 1996. The atypical neuroleptic profile of the glycine/*N*-methyl-D-aspartate receptor antagonist, L-701,324, in rodents. *J. Pharmacol. Exp. Ther.* 277, 578–585.
- Cai, Y.C., Ma, L., Fan, G.H., Zhao, J., Jiang, L.Z., Pei, G., 1997. Activation of *N*-methyl-D-aspartate receptor attenuates acute responsiveness of delta-opioid receptors. *Mol. Pharmacol.* 51, 583–587.
- Carlton, S.M., Coggeshall, R.E., 1999. Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res.* 820, 63–70.
- Carlton, S.M., Hargrett, G.L., 1995. Treatment with the NMDA antagonist memantine attenuates nociceptive responses to mechanical stimulation in neuropathic rats. *Neurosci. Lett.* 198, 115–118.
- Carlton, S.M., Hargrett, G.L., Coggeshall, R.E., 1995. Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. *Neurosci. Lett.* 197, 25–28.
- Carlton, S.M., Zhou, S.T., Coggeshall, R.E., 1998. Evidence for the interaction of glutamate and NK1 receptors in the periphery. *Brain Res.* 790, 160–169.
- Chaplan, S.R., Malmberg, A.B., Yaksh, T.L., 1997. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. *J. Pharmacol. Exp. Ther.* 280, 829–838.
- Chen, H.S.V., Pellegrini, J.W., Aggarwal, S.K., Lei, S.Z., Warach, S., Jensen, F.E., Lipton, S.A., 1992. Open-channel block of *N*-methyl-D-aspartate (NMDA) responses by memantine—therapeutic advantage against NMDA receptor-mediated neurotoxicity. *J. Neurosci.* 12, 4427–4436.
- Chen, J., Graham, S., Moroni, F., Simon, R., 1993. A study of the dose dependency of a glycine receptor antagonist in focal ischemia. *J. Pharmacol. Exp. Ther.* 267, 937–941.
- Chizh, B.A., Schlutz, H., Scheede, M., Englberger, W., 2000. The

- N*-methyl-D-aspartate antagonistic and opioid components of D-methadone antinociception in the rat spinal cord. *Neurosci. Lett.* 296, 117–120.
- Christensen, D., 1999. The antinociceptive effect of combined systemic administration of morphine and the glycine/NMDA receptor antagonist, (+)-HA-966 in a rat model of peripheral neuropathy (Vol. 125, p. 1641, 1998). *Br. J. Pharmacol.* 126, 1881.
- Coggeshall, R.E., Carlton, S.M., 1999. Evidence for an inflammation-induced change in the local glutamatergic regulation of postganglionic sympathetic efferents. *Pain* 83, 163–168.
- Collingridge, G.L., Bliss, T.V.P., 1995. Memories of NMDA receptors and LTP. *Trends Neurosci.* 18, 54–56.
- Danysz, W., Parsons, C.G., 1998. Glycine and *N*-methyl-D-aspartate receptors: physiological significance and possible therapeutic applications. *Pharmacol. Rev.* 50, 597–664.
- Davidson, E.M., Carlton, S.M., 1998. Intraplantar injection of dextrorphan, ketamine or memantine attenuates formalin-induced behaviors. *Brain Res.* 785, 136–142.
- Davidson, E.M., Coggeshall, R.E., Carlton, S.M., 1997. Peripheral NMDA and non-NMDA glutamate receptors contribute to nociceptive behaviors in the rat formalin test. *NeuroReport* 8, 941–946.
- Dickenson, A.H., 1990. A cure for wind up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol. Sci.* 11, 307–309.
- Dickenson, A.H., Chapman, V., Green, G.M., 1997. The pharmacology of excitatory and inhibitory amino acid-mediated events in the transmission and modulation of pain in the spinal cord. *Gen. Pharmacol.* 28, 633–638.
- Ebert, B., Andersen, S., Krogsgaardlarsen, P., 1995. Ketobemidone, methadone and pethidine are non-competitive *N*-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci. Lett.* 187, 165–168.
- Eide, P.K., Stubhaug, A., Oye, I., 1995. The NMDA-antagonist ketamine for prevention and treatment of acute and chronic post-operative pain. In: Breivik, H. (Ed.), *Baillieres Clinical Anaesthesiology International Practice and Research*. Tindall, London, pp. 539–554.
- Eisenberg, E., Vos, B.P., Strassman, A.M., 1993. The NMDA antagonist memantine blocks pain behavior in a rat model of formalin-induced facial pain. *Pain* 54, 301–307.
- Eisenberg, E., LaCross, S., Strassman, A.M., 1994. The effects of the clinically tested NMDA receptor antagonist memantine on carrageenan-induced thermal hyperalgesia in rats. *Eur. J. Pharmacol.* 255, 123–129.
- Eisenberg, E., LaCross, S., Strassman, A.M., 1995. The clinically tested *N*-methyl-D-aspartate receptor antagonist memantine blocks and reverses thermal hyperalgesia in a rat model of painful mononeuropathy. *Neurosci. Lett.* 187, 17–20.
- Elliott, K., Kest, B., Man, A., Kao, B., Inturrisi, C.E., 1995. *N*-methyl-D-aspartate (NMDA) receptors, mu and kappa opioid tolerance, and perspectives on new analgesic drug development. *Neuropsychopharmacology* 13, 347–356.
- Fan, G.H., Zhao, J., Wu, Y.L., Lou, L.G., Zhang, Z., Jing, Q., Ma, L., Pei, G., 1998. *N*-methyl-D-aspartate attenuates opioid receptor-mediated G protein activation and this process involves protein kinase C. *Mol. Pharmacol.* 53, 684–690.
- Frankiewicz, T., Potier, B., Bashir, Z.I., Collingridge, G.L., Parsons, C.G., 1996. Effects of memantine and (+)-MK-801 on NMDA-induced currents in cultured neurones and on synaptic transmission and LTP in area CA1 of rat hippocampal slices. *Br. J. Pharmacol.* 117, 689–697.
- Gordon, S.M., Dubner, R., Dionne, R.A., 1999. Antihyperalgesic effect of the *N*-methyl-D-aspartate receptor antagonist dextromethorphan in the oral surgery model. *J. Clin. Pharmacol.* 39, 139–146.
- Gorman, A.L., Elliott, K.J., Inturrisi, C.E., 1997. The D- and L-isomers of methadone bind to the non-competitive site on the *N*-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci. Lett.* 223, 5–8.
- Hansel, C., Artola, A., Singer, W., 1996. Different threshold levels of postsynaptic [Ca²⁺ + Ki] have to be reached to induce LTP and LTD in neocortical pyramidal cells. *J. Physiol. (Paris)* 90, 317–319.
- Hargreaves, R.J., Rigby, M., Smith, D., Hill, R.G., 1993. Lack of effect of L-687,414 ((+)-cis-4-methyl-HA-966), an NMDA receptor antagonist acting at the glycine site, on cerebral glucose metabolism and cortical neuronal morphology. *Br. J. Pharmacol.* 110, 36–42.
- Herrero, J.F., Laird, J.M.A., LopezGarcia, J.A., 2000. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog. Neurobiol.* 61, 169–203.
- Herron, C.E., Lester, R.A.J., Coan, E.J., Collingridge, G.L., 1986. Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism. *Nature* 322, 265–269.
- Hewitt, D.J., 2000. The use of NMDA-receptor antagonists in the treatment of chronic pain. *Clin. J. Pain* 16, S73–S79.
- Houghton, A.K., Parsons, C.G., Headley, P.M., 2001. MRZ 2/579, a fast kinetic NMDA receptor antagonist, delays the development of morphine tolerance in awake rats. *Pain* 91, 201–207.
- Ilkjaer, S., Dirks, J., Brennum, J., Wernberg, M., Dahl, J.B., 1997. Effect of systemic *N*-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *Br. J. Anaesth.* 79, 600–605.
- Jackson, D.L., Graff, C.B., Richardson, J.D., Hargreaves, K.M., 1995. Glutamate participates in the peripheral modulation of thermal hyperalgesia in rats. *Eur. J. Pharmacol.* 284, 321–325.
- Karcz-Kubicha, M., Wedzony, K., Zajackowski, W., Danysz, W., 1999. NMDA receptor antagonists acting at the glycine(B) site in rat models for antipsychotic-like activity. *J. Neural Transm.* 106, 1189–1204.
- Kolesnikov, Y.A., Maccellini, M.L., Pasternak, G.W., 1994. 1-aminocyclopropane carboxylic acid (ACPC) prevents mu and delta opioid tolerance. *Life Sci.* 55, 1393–1398.
- Kornhuber, J., Weller, M., 1997. Psychotogenicity and *N*-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. *Biol. Psychiatry* 41, 135–144.
- Laird, J.M.A., de la Rubia, P.G., Cervero, F., 1995. Excitability changes of somatic and viscerosomatic nociceptive reflexes in the decerebrate-spinal rabbit: role of NMDA receptors. *J. Physiol.* 489, 545–555.
- Laird, J.M.A., Mason, G.S., Webb, J., Hill, R.G., Hargreaves, R.J., 1996. Effects of a partial agonist and a full antagonist acting at the glycine site of the NMDA receptor on inflammation-induced mechanical hyperalgesia in rats. *Br. J. Pharmacol.* 117, 1487–1492.
- Lawand, N.B., Willis, W.D., Westlund, K.N., 1997. Excitatory amino acid receptor involvement in peripheral nociceptive transmission in rats. *Eur. J. Pharmacol.* 324, 169–177.
- Löscher, W., Wlaz, P., Rundfeldt, C., Baran, H., Honack, D., 1994. Anticonvulsant effects of the glycine/NMDA receptor ligands d-cycloserine and d-serine but not R(+)-HA-966 in amygdala-kindled rats. *Br. J. Pharmacol.* 112, 97–106.
- Lutty, K., Shen, K.Z., Kwon, I.S., Cai, S.X., Woodward, R.M., Keana, J.F.W., Weber, E., 1995. Blockade of morphine tolerance by ACEA-1328, a novel NMDA receptor glycine site antagonist. *Eur. J. Pharmacol.* 273, 187–189.
- Lutty, K., Shen, K.Z., Woodward, R.M., Weber, E., 1996. Inhibition of morphine tolerance by NMDA receptor antagonists in the formalin test. *Brain Res.* 731, 171–181.
- Malenka, R.C., 1994. Synaptic plasticity in the hippocampus: LTP and LTD. *Cell* 78, 535–538.
- Mao, J.R., 1999. NMDA and opioid receptors: their interactions in antinociception, tolerance and neuroplasticity. *Brain Res. Rev.* 30, 289–304.
- Mao, J.R., Price, D.D., Hayes, R.L., Lu, J., Mayer, D.J., Frenk, H., 1993. Intrathecal treatment with dextrorphan or ketamine potentially reduces pain-related behaviors in a rat model of peripheral mononeuropathy. *Brain Res.* 605, 164–168.
- Mao, J.R., Price, D.D., Mayer, D.J., 1995. Experimental mononeuropathy reduces the antinociceptive effects of morphine: implications for common intracellular mechanisms involved in morphine tolerance and neuropathic pain. *Pain* 61, 353–364.

- McRoberts, J.A., Coutinho, S.V., Marvizon, J.C., Grady, E.F., Tognetto, M., Sengupta, J.N., Ennes, H.S., Chaban, V.V., Amadesi, S., Creminon, C., Lanthorn, T., Geppetti, P., Bunnett, N.W., Mayer, E.A., 2001. Role of peripheral *N*-methyl-D-aspartate (NMDA) receptors in visceral nociception in rats. *Gastroenterology* 120, 1737–1748.
- Mealing, G.A.R., Lanthorn, T.H., Small, D.L., Black, M.A., Laferriere, N.B., Morley, P., 1997. Antagonism of *N*-methyl-D-aspartate-evoked currents in rat cortical cultures by ARL 15896AR. *J. Pharmacol. Exp. Ther.* 281, 376–383.
- Mikkelsen, S., Ilkjaer, S., Brennum, J., Borgbjerg, F.M., Dahl, J.B., 1999. The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. *Anesthesiology* 90, 1539–1545.
- Millan, M.J., Seguin, L., 1994. Chemically-diverse ligands at the glycineB site coupled to *N*-methyl-D-aspartate (NMDA) receptors selectively block the late phase of formalin-induced pain in mice. *Neurosci. Lett.* 178, 139–143.
- Neugebauer, V., Kornhuber, J., Lucke, T., Schaible, H.G., 1993. The clinically available NMDA receptor antagonist memantine is antinociceptive on rat spinal neurones. *NeuroReport* 4, 1259–1262.
- Olivar, T., Laird, J.M., 1999. Differential effects of *N*-methyl-D-aspartate receptor blockade on nociceptive somatic and visceral reflexes. *Pain* 79, 67–73.
- Omote, K., Kawamata, T., Kawamata, M., Namiki, A., 1998. Formalin-induced release of excitatory amino acids in the skin of the rat hindpaw. *Brain Res.* 787, 161–164.
- Parsons, C.G., Danysz, W., Quack, G., Hartmann, S., Lorenz, B., Woltenburg, C., Baran, L., Przegalinski, E., Kostowski, W., Krzascik, P., Chizh, B., Headley, P.M., 1997. Novel systemically active antagonists of the glycine site of the *N*-methyl-D-aspartate receptor: electrophysiological, biochemical and behavioral characterization. *J. Pharmacol. Exp. Ther.* 283, 1264–1275.
- Parsons, C.G., Danysz, W., Quack, G., 1998. Glutamate in CNS Disorders as a target for drug development. An update. *Drug News Perspect.* 11, 523–569.
- Parsons, C.G., Danysz, W., Quack, G., 1999. Memantine is a clinically well tolerated *N*-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data. *Neuropharmacology* 38, 735–767.
- Pasternak, G.W., Inturrisi, C.E., 1995. Pharmacological modulation of opioid tolerance. *Exp. Opin. Invest. Drugs* 4, 271–281.
- Popik, P., Danysz, W., 1997. Inhibition of reinforcing effects of morphine and motivational aspects of naloxone-precipitated opioid withdrawal by *N*-methyl-D-aspartate receptor antagonist, memantine. *J. Pharmacol. Exp. Ther.* 280, 854–865.
- Popik, P., Kozela, E., 1999. Clinically available NMDA antagonist, memantine, attenuates tolerance to analgesic effects of morphine in a mouse tail flick test. *Pol. J. Pharmacol.* 51, 223–231.
- Popik, P., Skolnick, P., 1996. The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence. *Pharmacol. Biochem. Behav.* 53, 791–797.
- Popik, P., Mamczarz, J., Fraczek, M., Widla, M., Hesselink, M., Danysz, W., 1998. Inhibition of reinforcing effects of morphine and naloxone-precipitated opioid withdrawal by novel glycine site and uncompetitive NMDA receptor antagonists. *Neuropharmacology* 37, 1033–1042.
- Price, D.D., Mao, J.R., Frenk, H., Mayer, D.J., 1994. The *N*-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 59, 165–174.
- Qian, J., Brown, S.D., Carlton, S.M., 1996. Systemic ketamine attenuates nociceptive behaviors in a rat model of peripheral neuropathy. *Brain Res.* 715, 51–62.
- Quartaroli, M., Carignani, C., DalForno, G., Mugnaini, M., Ugolini, A., Arban, R., Bettelini, L., Maraia, G., Belardetti, F., Reggiani, A., Trist, D.G., Ratti, E., DiFabio, R., Corsi, M., 1999. Potent antihyperalgesic activity without tolerance produced by glycine site antagonist of *N*-methyl-D-aspartate receptor GV196771A. *J. Pharmacol. Exp. Ther.* 290, 158–169.
- Ren, K., 1994. Wind-up and the NMDA receptor: from animal studies to humans. *Pain* 59, 157–158.
- Ren, K., Williams, G.M., Hylden, J.L.K., Ruda, M.A., Dubner, R., 1992. The intrathecal administration of excitatory amino acid receptor antagonists selectively attenuated carrageenan-induced behavioral hyperalgesia in rats. *Eur. J. Pharmacol.* 219, 235–243.
- Rogawski, M.A., 1993. Therapeutic potential of excitatory amino acid antagonists—channel blockers and 2,3-benzodiazepines. *Trends Pharmacol. Sci.* 14, 325–331.
- Sandkuhler, J., Liu, X.G., 1998. Induction of long-term potentiation at spinal synapses by noxious stimulation or nerve injury. *Eur. J. Neurosci.* 10, 2476–2480.
- Schmid, R.L., Sandler, A.N., Katz, J., 1999. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain* 82, 111–125.
- Semenova, S., Danysz, W., Bessalov, A., 1999. Low-affinity NMDA receptor channel blockers inhibit acquisition of intravenous morphine self-administration in naive mice. *Eur. J. Pharmacol.* 378, 1–8.
- Suzuki, R., Matthews, E.A., Dickenson, A.H., 2001. Comparison of the effects of (+)-MK-801, ketamine and memantine on responses of spinal dorsal horn neurones in a rat model of mononeuropathy. *Pain* 91, 101–109.
- Swope, S.L., Moss, S.I., Raymond, L.A., Haganir, R.L., 1999. Regulation of ligand-gated ion channels by protein phosphorylation. *Adv. Second Messenger Phosphoprotein Res.* 33, 49–78.
- Taniguchi, K., Shinjo, K., Mizutani, M., Shimada, K., Ishikawa, T., Menniti, F.S., Nagahisa, A., 1997. Antinociceptive activity of CP-101,606, an NMDA receptor NR2B subunit antagonist. *Br. J. Pharmacol.* 122, 809–812.
- Tatlisumak, T., Takano, K., Meiler, M.R., Fisher, M., 1998. A glycine site antagonist, ZD9379, reduces number of spreading depressions and infarct size in rats with permanent middle cerebral artery occlusion. *Stroke* 29, 190–195.
- Trujillo, K.A., 2000. Are NMDA receptors involved in opiate-induced neural and behavioral plasticity? A review of preclinical studies. *Psychopharmacology* 151, 121–141.
- Trujillo, K.A., Akil, H., 1991. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist (+)-MK-801. *Science* 251, 85–87.
- Trujillo, K.A., Akil, H., 1995. Excitatory amino acids and drugs of abuse: a role for *N*-methyl-D-aspartate receptors in drug tolerance, sensitization and physical dependence. *Drug Alcohol Depend.* 38, 139–154.
- Vaccarino, A.L., Marek, P., Kest, B., Weber, E., Keana, J.F.W., Liebeskind, J.C., 1993. NMDA receptor antagonists, MK-801 and ACEA-1011, prevent the development of tonic pain following subcutaneous formalin. *Brain Res.* 615, 331–334.
- Warnecke, T., Jorum, E., Stubhaug, A., 1997. Local treatment with the *N*-methyl-D-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. *Neurosci. Lett.* 227, 1–4.
- Yaksh, T.L., 1989. Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain* 37, 111–123.
- Zhou, S.T., Bonasera, L., Carlton, S.M., 1996. Peripheral administration of NMDA, AMPA or KA results in pain behaviors in rats. *NeuroReport* 7, 895–900.